

Structural Studies on Benzothiazoles. Crystal and Molecular Structure of 5,6-Dimethoxy-2-(4-methoxyphenyl)-benzothiazole and Molecular Orbital Calculations on Related Compounds¹.

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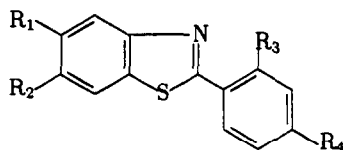
Abstract

The benzothiazole derivatives reported here have structural similarities to the 2-phenylindole derivatives that are known to bind to oestrogen receptors. We report the synthesis of 5,6-dimethoxy-2-(4-methoxyphenyl)-benzothiazole together with the determination of its three dimensional crystal structure. Crystals are monoclinic, space group $P2_1/c$, $a=17.142(1)$, $b=11.165(1)$, $c=7.683(2)$ Å, $\beta=101.34(1)^\circ$. 2307 Reflections were refined to $R=0.039$. The inter-ring twist angle is 21° , greater than in 2-(*o*-hydroxyphenyl)benzothiazole but similar to that in 2-(4'-bromophenyl)-4,6-dimethoxyindole. Molecular mechanics calculations predict a torsional barrier to inter-ring twist of $6.3 \text{ kcal mol}^{-1}$ for unsubstituted benzothiazole. Molecular orbital calculations show that while hydrogen bonding can confer stability on substituted benzothiazoles, a greater number of non-hydrogen bonding groups as substituents can confer even greater stability.

¹Supplementary data available (atomic thermal parameters, structure factors). See Notice to Authors. Tetrahedron, 40(2), n (1984).

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Hydroxy-substituted 2-phenylindoles have been shown to have high relative binding affinities for the oestrogen receptor and thus have potential for the treatment of hormone dependent breast cancer¹. A systematic study of a series of 2-phenylindole derivatives has considered binding affinity for the oestrogen receptor, mammary tumour inhibiting activity and oestrogenic and anti-oestrogenic properties¹. It is possible that benzothiazole compounds (compound (1) and its derivatives) having a similar ring structure will show related activity, and in this paper we look at the structures of a number of these compounds. The crystal structure of a simple benzothiazole compound has been determined (compound (2))², but this structure is complicated by the presence of an intramolecular hydrogen bond.



Compound	R ₁	R ₂	R ₃	R ₄
(1)	H	H	H	H
(2)	H	H	OH	H
(3)	OCH ₃	OCH ₃	H	OCH ₃

5,6-dimethoxy-2-(4-methoxyphenyl)-benzothiazole (3) was synthesised via the Jacobsen method³ from the corresponding trimethoxy thioamide. This benzothiazole is intended to act as the precursor to a series of substituted benzothiazoles, and we report its three dimensional crystal structure as determined by X-ray diffraction.

CRYSTAL AND MOLECULAR STRUCTURE OF (3)

The crystal had dimensions 0.35 x 0.35 x 1.25 mm. The data were collected on an Enraf-Nonius CAD4 diffractometer with monochromated Mo-K_α radiation, $\lambda = 0.71069 \text{ \AA}$, C₁₆H₁₅NO₃S, $M = 301.4$, monoclinic, $a = 17.142(1)$, $b = 11.165(1)$, $c = 7.683(2) \text{ \AA}$, $\beta = 101.34(1)^\circ$, $V = 1441.7(9) \text{ \AA}^3$, $Z = 4$, $D_m = 1.35(2) \text{ g cm}^{-3}$, $D_x = 1.39 \text{ g cm}^{-3}$, $F(000) = 632$, $\mu(\text{Mo-K}\alpha) = 1.88 \text{ cm}^{-1}$, space group $P2_1/c$. The 3134 intensity data were collected by the ω - 2θ scan technique, and of these 2307 reflections were

deemed observed with $|F_o| > 2.5\sigma$. Using SHELX-76⁴, an E-map was produced in which all but four of the non-hydrogen atoms were located. These remaining atoms were located in a subsequent Fourier map. Hydrogen atoms were included in calculated positions and all atoms refined isotropically. Further refinement with anisotropic non-hydrogen atoms reduced the unweighted discrepancy index to $R = 0.039$ ($R_w = 0.046$). In the latter stages of refinement, reflections were weighted according to $w = K/[\sigma^2(F) + 0.003F^2]$. Full-matrix refinement was used, with the quantity $\sum w(F_o - F_c)^2$ being minimised. Refinement was terminated with the maximum value of shift/e.s.d. being 0.031. Finally a difference electron density map was calculated which showed no feature greater than $0.28 \text{ e } \text{Å}^{-3}$. Calculations were performed on the VAX 8650 Cluster at Aston University. Observed and calculated structure factors, and atom thermal parameters are given in a Supplementary Publication. Scattering factors were taken from reference 5.

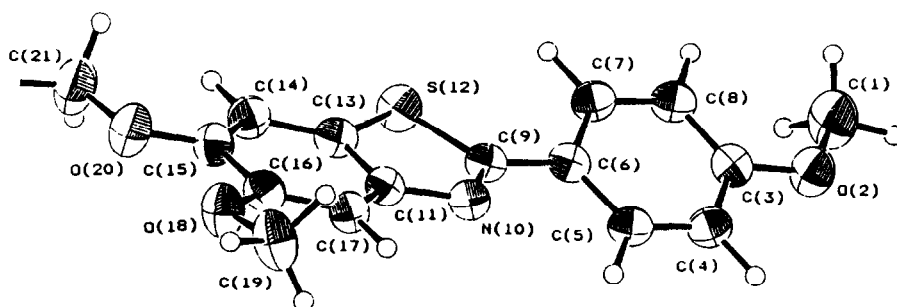


Figure 1: Crystal structure of 5,6-dimethoxy-2-(4-methoxyphenyl)-benzothiazole (2) as determined by X-ray diffraction

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Atomic coordinates are given in Table 1, and a molecule of (3) is shown in Figure 1 which was produced with the ORTEP program⁶ on the Amdahl 5890-300 computer at the Manchester

Table 1. Final atomic coordinates ($\times 10^4$) for (3) with estimated standard deviations in parentheses.

Atom	x/a	y/b	z/c	Atom	x/a	y/b	z/c
C(1)	-2210(2)	3059(3)	-1640(4)	C(19)	3817(1)	5172(3)	9944(3)
O(2)	-1921(1)	3803(1)	-0154(2)	O(20)	4840(1)	3733(2)	6228(2)
C(3)	-1124(1)	3773(2)	0531(3)	C(21)	5246(1)	3157(3)	5010(4)
C(4)	-0840(1)	4664(2)	1774(3)	H(40)	-1245(1)	5323(2)	2119(3)
C(5)	-0050(1)	4707(2)	2549(2)	H(50)	0164(1)	5401(2)	3502(2)
C(6)	0489(1)	3861(2)	2115(2)	H(70)	0597(1)	2314(2)	0545(3)
C(7)	0193(1)	2975(2)	0891(3)	H(80)	-0818(1)	2227(2)	-0846(3)
C(8)	-0601(1)	2925(2)	0098(3)	H(101)	-2827(2)	3237(3)	-2206(4)
C(9)	1326(1)	3918(2)	2974(2)	H(102)	-2146(2)	2141(3)	-1194(4)
N(10)	1593(1)	4455(1)	4482(2)	H(103)	-1854(2)	3208(3)	-2633(4)
C(11)	2410(1)	4326(2)	4980(2)	H(140)	3865(1)	2985(2)	3189(3)
S(12)	2053(0)	3225(0)	2000(1)	H(170)	2596(1)	5198(2)	7541(3)
C(13)	2772(1)	3685(2)	3786(3)	H(191)	4317(1)	5227(3)	11043(3)
C(14)	3592(1)	3466(2)	4132(3)	H(192)	3407(1)	4495(3)	10218(3)
C(15)	4038(1)	3877(2)	5712(3)	H(193)	3518(1)	6028(3)	9766(3)
C(16)	3669(1)	4487(2)	6963(3)	H(211)	5878(1)	3155(3)	5539(4)
C(17)	2870(1)	4718(2)	6597(3)	H(212)	5131(1)	3601(3)	3736(4)
O(18)	4175(1)	4790(2)	8514(2)	H(213)	5033(1)	2245(3)	4852(4)

Computing Centre. Geometric parameters are given in Table 2, showing that the C-O distances are much as expected at around 1.424 Å. C-C bond lengths within the isolated phenyl ring range from 1.368 to 1.404 Å with an average of 1.388 Å, while in the benzothiazole moiety they average 1.396 Å with a range from 1.368 to 1.423 Å. The C(6)-C(9) inter-ring bond length of 1.457(3) Å is rather shorter than the 1.487 Å expected for biphenyl compounds⁷ and that observed in (2). The N(10)-C(11) and S(12)-C(13) lengths of 1.385 and 1.732 Å respectively are both shorter than the corresponding value found in (2), but other N-C and S-C bond lengths show a closer agreement.

The bond angles are largely unexceptional, but the angles around the ether oxygens are considerably greater than tetrahedral, being approximately 117°. In the six membered ring of the benzothiazole and the 2-phenyl ring, angles range from 115.7 to 124.7° and from 109.4 to 129.0° respectively, with the corresponding averages being close to the ideal at 120.3 and 119.4°. The angle made at the sulphur atom is, as expected, lower at 89.2°. Table 2 shows that the inter-ring twist angle about the C(6)-C(9) bond is 21°, suggesting a considerable loss of conjugation. This is comparable to the value of 29° in 2-(4'-bromophenyl)-4,6-dimethoxyindole⁸. The torsion angles about the C-O bonds also differ from their ideal values by up to 13°; this is not too surprising in view of the lower barrier to rotation about these single bonds. The molecule contains no potential hydrogen bonding groups, but there are a number of interatomic contacts at distances less than the sum of the van

Table 2. Geometric parameters in (3). Lengths in Å and angles in degrees.

C(1)-O(2)	1.420(3)	N(10)-C(11)	1.385(2)
O(2)-C(3)	1.364(2)	C(11)-C(13)	1.401(3)
C(3)-C(4)	1.398(3)	C(11)-C(17)	1.404(3)
C(3)-C(8)	1.388(3)	S(12)-C(13)	1.732(2)
C(4)-C(5)	1.368(3)	C(13)-C(14)	1.400(3)
C(5)-C(6)	1.407(3)	C(14)-C(15)	1.380(3)
C(6)-C(7)	1.391(2)	C(15)-C(16)	1.423(3)
C(6)-C(9)	1.457(3)	C(15)-O(20)	1.363(2)
C(7)-C(8)	1.379(3)	C(16)-C(17)	1.368(3)
C(9)-N(10)	1.305(2)	C(16)-O(18)	1.372(2)
C(9)-S(12)	1.754(2)	O(18)-C(19)	1.425(3)
O(20)-C(21)	1.426(3)		
C(1)-O(2)-C(3)	117.5(2)	N(10)-C(11)-C(13)	115.2(2)
O(2)-C(3)-C(4)	115.7(2)	C(13)-C(11)-C(17)	119.7(2)
O(2)-C(3)-C(8)	124.7(2)	C(9)-S(12)-C(13)	89.2(1)
C(3)-C(4)-C(5)	120.2(2)	C(11)-C(13)-S(12)	109.4(1)
C(4)-C(5)-C(6)	120.9(2)	C(11)-C(13)-C(14)	121.5(2)
C(5)-C(6)-C(7)	117.9(2)	S(12)-C(13)-C(14)	129.0(2)
C(5)-C(6)-C(9)	119.8(2)	C(13)-C(14)-C(15)	118.1(2)
C(7)-C(6)-C(9)	122.2(2)	C(14)-C(15)-C(16)	120.7(2)
C(6)-C(7)-C(8)	121.7(2)	C(14)-C(15)-O(20)	124.7(2)
C(3)-C(8)-C(7)	119.6(2)	C(16)-C(15)-O(20)	114.6(2)
C(6)-C(9)-N(10)	124.4(2)	C(15)-C(16)-C(17)	120.8(2)
C(6)-C(9)-S(12)	120.4(1)	C(15)-C(16)-O(18)	114.6(2)
N(10)-C(9)-S(12)	115.2(1)	C(11)-C(17)-C(16)	119.2(2)
C(9)-N(10)-C(11)	110.9(2)	C(16)-O(18)-C(19)	116.7(2)
N(10)-C(11)-C(17)	125.0(2)	C(15)-O(20)-C(21)	117.2(2)
C(4)-C(3)-C(8)	119.6(2)		
C(5)-C(6)-C(9)-N(10)	21.3	C(7)-C(6)-C(9)-N(10)	-157.3
C(5)-C(6)-C(9)-S(12)	-159.4	C(7)-C(6)-C(9)-S(12)	22.0
O(18) ... O(18) [1-x,1-y,1-z]	3.301		
O(18) ... C(19) [1-x,1-y,1-z]	3.414		
O(2) ... S(12) [1-x,1-y,1-z]	3.598		
S(12) ... S(12) [x,0.5-y,0.5+z]	4.169		
N(10) ... S(12) [x,0.5-y,0.5+z]	3.566		
S(12) ... C(17) [x,0.5-y,0.5+z]	3.609		
C(11) ... S(12) [x,0.5-y,0.5+z]	3.357		
S(12) ... C(13) [x,0.5-y,0.5+z]	3.656		

der Waals' radii, in particular involving the sulphur atom. These indicate a fairly tightly packed structure. A stereo view of the molecule is shown in Figure 2.

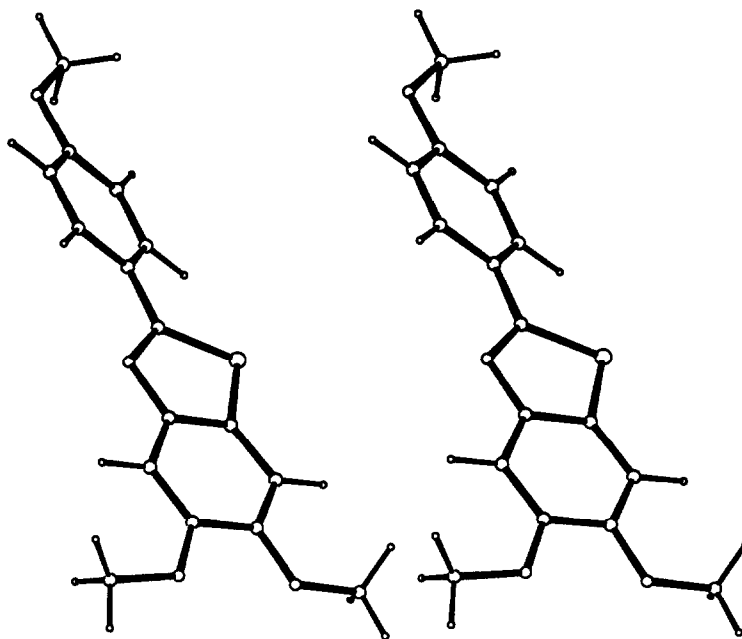


Figure 2: Stereo view of 5,6- dimethoxy-2-(4-methoxyphenyl)-benzothiazole (3)

MOLECULAR MECHANICS AND MOLECULAR ORBITAL CALCULATIONS

Our crystallographic results show a significant twist between the two ring systems in compound (3). This compares with compound (2) where the rings are planar, but as noted earlier this may well be due to the presence of a strong intramolecular hydrogen bond. This feature in (2) makes comparison difficult, so we have investigated this aspect of the benzothiazole structures further through the use of molecular mechanics and molecular orbital calculations.

A model of (1) was built by modifying the crystal structure of (3) with the Chem-X program⁹, and the dihedral driver option of the MM2 molecular mechanics program¹⁰ was used to drive the inter-ring torsion angle through 360°. The resulting plot of steric energy against torsion angle is

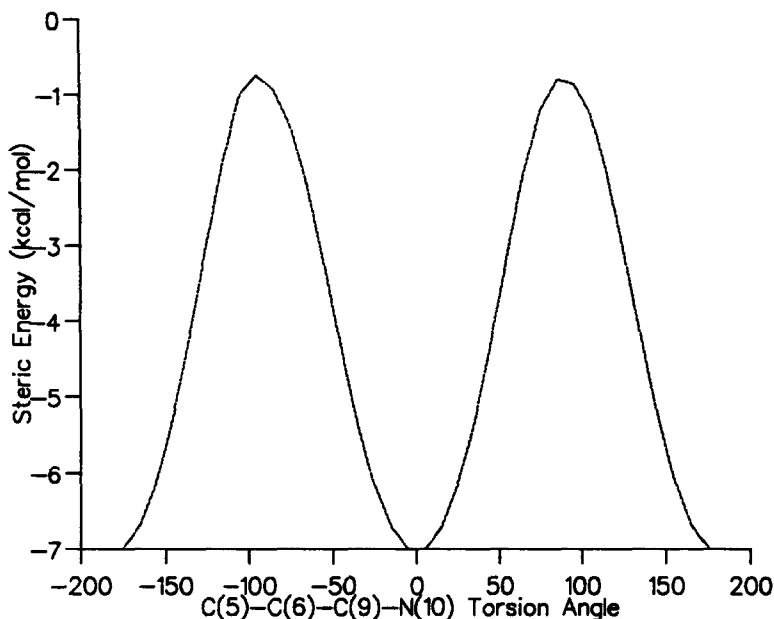


Figure 3: Graph of Steric Energy versus inter-ring Torsion Angle for Compound (1).

shown in Figure 3. This predicts a planar structure for the unsubstituted benzothiazole molecule (1), leading to maximum conjugation in the absence of hydrogen bonding or steric interaction effects. The calculations also predict a torsional barrier to rotation of $6.3 \text{ kcal mol}^{-1}$ in this molecule.

Molecular orbital calculations were then performed on the planar conformation of (1) together with the crystal structure conformations of (2) and (3). The STO-3G basis set was used with the GAUSSIAN86 program¹¹. The size of these molecules precludes the use of more elaborate basis sets. The resulting partial atomic charges, dipole moments and Restricted Hartree Fock energies are given in Table 3.

The charges on the nitrogen and sulphur atoms are considerably larger than those on the carbons in all three molecules, and are approximately equal in magnitude in (1) and (3). However in (2) the presence of hydrogen bonding results in a larger negative charge on the nitrogen atom. The smallest charges on carbon atoms result for those in the inter-ring bond, and negative charges result for the bridgehead carbon adjacent to the nitrogen atom and for those which have non-hydrogen substituents attached. The trend in dipole moments seen is consistent with the number of substituents in each

Table 3. Atomic charges from molecular orbital calculations.

Atom	(1)	(2)	(3)
C(3)	-0.06	-0.08	0.14
C(4)	-0.06	-0.15	-0.08
C(5)	-0.05	0.19	-0.04
C(6)	-0.01	-0.06	-0.02
C(7)	-0.06	-0.06	-0.05
C(8)	-0.06	-0.08	-0.10
C(9)	0.01	0.03	0.01
N(10)	-0.27	-0.32	-0.27
C(11)	0.06	0.07	0.06
S(12)	0.24	0.24	0.23
C(13)	-0.11	-0.10	-0.11
C(14)	-0.07	-0.09	-0.10
C(15)	-0.06	-0.09	0.13
C(16)	-0.07	-0.08	0.11
C(17)	-0.06	-0.07	-0.09
Dipole moment(D)	1.29	2.46	2.98
RHF Energy (AU)	-938.41	-1012.09	-1275.66

molecule. Hydrogen bonding clearly provides considerable electronic stability for (2) compared to (1), but it is noteworthy that the more highly substituted (3) has a lower RHF energy than either.

CONCLUSIONS

The preferred conformation of benzothiazole compounds is very dependent on the number and nature of the substituents present. A planar structure is preferred for unsubstituted compounds and for those which can form hydrogen bonds in such a conformation. However, greater electronic stability may be obtained by increasing the number of substituents, even if they do not exhibit hydrogen bonding properties.

EXPERIMENTAL PROCEDURE

U v. spectra were recorded on a Pye Unicam SP8000 Ultraviolet Recording Spectrophotometer, i.r. spectra on a Perkin-Elmer 1310 Infrared Spectrophotometer and 300 MHz n.m.r. spectra on a Bruker AC300 NMR Spectrometer. The t.l.c. systems employed Kieselgel 60F254 (0.25 mm) as the absorbant. Melting points are uncorrected.

3,4,4'-Trimethoxythiobenzanilide: 3,4,4'- trimethoxybenzanilide was obtained by stirring 4-aminoveratrole with an equimolar ratio of 4- methoxybenzoyl chloride in pyridine (1 h) washing the product with water and recrystallising from methanol. A mixture of 3,4,4'-trimethoxybenzanilide (4.00 g) and Lawesson's reagent (2.82g) was refluxed (1 h) in chlorobenzene. After cooling the solid produced was filtered off and recrystallised from methanol to yield yellow crystals, m.p. 139-140°C (Found : C, 63.2; H, 5.5; N, 4.9%; M+, 303. C₁₆H₁₇NO₃S requires C, 63.4; H, 5.6; N, 4.6%); ν_{max} (nujol) 3160 (NH), 1590 cm⁻¹; δ (CDCl₃) 8.96 (1H,s), 7.83 (2H,d), 7.47 (1H,s), 7.08 (1H,d), 6.86 (3H,t), 3.86 (3H,s), 3.85 (3H,s), 3.83 (3H,s) ppm; λ_{max} (EtOH) 219, 263, 337 nm; R_f (CH₃Cl) 0.24.

5,6-Dimethoxy-2-(4-methoxyphenyl)benzothiazole (3) - A suspension of finely divided 3,4,4'-trimethoxythiobenzanilide (1.00 g) in 10% NaOH_(aq) (21 ml) was added slowly to a stirred solution of potassium ferricyanide (4.34 g) in water (15 ml), maintained at 80-85°C. The mixture was heated for a further hour then cooled to room temperature and stirred overnight. The solid produced was filtered, washed and recrystallised from methanol to give cream needle crystals, m.p. 159-160 °C (Found: C, 63.7; H, 5.0; N, 4.7%; M+, 301. C₁₆H₁₅NO₃S requires C, 63.8; H, 5.0; N, 4.7%); ν_{max} (nujol) 1590, 1280, 1240, 1210, 1150, 830 cm⁻¹; δ (CDCl₃) 7.93 (2H,d), 7.49 (1H,s), 7.25 (1H,s), 6.90 (2H,d), 3.94 (3H,s), 3.93 (3H,s), 3.84 (3H,s) ppm; λ_{max} (EtOH) 239, 354 nm; R_f (CHCl₃) 0.20.

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REFERENCES

1. Von Angerer, E.; Prekajak, J. *J. Med. Chem.* **1983**, *26*, 113; von Angerer, E.; Prekajak, J.; Strohmeier, J. *J. Med. Chem.* **1984**, *27*, 1439.
2. Sténson, P. *Acta Chem. Scand.* **1970**, *24*, 3729.
3. Potts, K.T. in *Comprehensive Heterocyclic Chemistry. The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds* eds Katritzky, A.R.; Rees, C.W.; Pergamon Press Ltd., Oxford, **1984**, *5*, 111.
4. Sheldrick, G.M. *SHELX-76, Program for Crystal Structure Determinations*, **1976**, University of Cambridge.
5. *International Tables for X-Ray Crystallography*, **1974**, *4*, Kynoch Press, Birmingham.
6. Johnson, C.K. *ORTEP, Oak Ridge Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations*, **1976**, Oak Ridge National Laboratory.
7. Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1.
8. Black, D.St.C.; Gatehouse, B.M.K.C.; Théobald, F.; Wong, L.C.H. *Aust. J. Chem.* **1980**, *33*, 343.
9. *Chem-X*, developed and distributed by Chemical Design Ltd., Oxford.
10. Allinger, N.L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.
11. Frisch, M.J.; Binkley, J.S.; Schlegel, H.B.; Raghavachari, K.; Melius, C.F.; Martin, R.L.; Stewart, J.J.P.; Bobrowicz, F.W.; Rohlfing, C.M.; Kahn, L.R.; Defrees, D.J.; Seeger, R.; Whiteside, R.A.; Fox, D.J.; Fleuder, E.M.; Pople, J.A. *Gaussian 86*, **1984**, Carnegie-Mellon Quantum Chemistry Publishing Unit, Pittsburgh PA.